Applicants respectfully request reconsideration of the pending rejection and reexamination of the present claims in light of the amendments and the remarks detailed below. By these amendments, the Applicants do not acquiesce to the propriety of any of the Examiner's rejections and do not disclaim any subject matter to which Applicants are entitled.

Claim Rejections under 35 U.S.C. §112 should be withdrawn

Claims 1-39 are rejected under 35 U.S.C §112, first paragraph, for alleged lack of enablement. Applicants respectfully disagree with the Examiner and submit that the rejected claims are fully enabled. As pointed out by the examiner, an exemplary method for predicting hybridization intensity is provided, in at least claim 3 and the specification (e.g. pages 3, 4 and 6). In Claim 3:

$$Ln(I) = \sum_{i=1}^{3N} W_i S_i$$

Or

$$Ln(I) = \sum_{i=1}^{3N} W_i S_i + C_2$$

The Examiner points out that neither the value of the constant "C_2" nor the means to determine its value are provided. Applicants respectfully submit that the value of C_2 may be determined by multiple linear regression using a training data set (see below).

The Office Action further alleges that the value of the weight coefficient W_i is not provided and in embodiments where W_i may be determined by multiple linear regression analysis, the data being analyzed is not provided. In the specification and (e.g.) claim 4,

Applicants explain that the weight coefficient W_i is determined using multiple linear regression analysis. In a multiple linear regression analysis, the weight coefficient W_i and constant (e.g. C_2) can be resolved simultaneously, using, for example, a training data set (see, e.g. Example 1, pages 32-33, where the training data set is yeast Latin Square data; see also Figure 14 which depicts a process for obtaining weight coefficients). Multiple linear regression is a common practice, well known to one of ordinary skill in the art at the time of the application and is also described in the specification (e.g. pages 19 and 20).

In another embodiment that describes a physical model to predict hybridization intensities, the value of W_i may be determined by empirical data (support found on page 16 and Figure 3 of the specification). This has also been pointed out by the Examiner, who however feels that the claims encompass much more than the physical model and no explicit algorithm is provided to arrive at a value for W_i. Applicants respectfully submit that the claims were not limited to the physical model alone because the value of W_i can be derived by other methods, e.g. by multiple linear regression analysis.

Equations 4-8 on page 19 of the specification provide an approach to arrive at a value for W_i. Specifically equation 8 states that $W_i = C_1P_i$. The Examiner notes that the information on page 19 is a particular multiple linear regression model with respect to a reference base such as A and the claims are not limited to the simple hybridization scheme of Figure 4, the relationships set forth in Equations 4-8, or the necessity for a training data set from experimental data as disclosed on page 20. The Examiner further notes that the assumption that $W_i = C_1P_i$ is not a limitation of the claims. Applicants respectfully submit that one skilled in the art will realize that the model can be extrapolated to bases other than A, hence it is not

necessary for the claims to be limited to the particular multiple linear regression model described on page 19.

The Examiner notes that line 4 of page 19 recites C_2, which does not appear to be associated with any equation. The Applicants have addressed this objection by removing C_2.

The Examiner deems confusing, the model for probes of N bases (in length) set forth on page 19, following equation 8. Applicants respectfully submit that this is standard linear regression model well known to one of ordinary skill in the art. The Examiner is referred back to claim 3, which recites the equation for determining hybridization intensity – the present model (on page 19) is not inconsistent with the equation in claim 3.

The Examiner notes that the subscripting notation [i.e. $Ln(I_1) = W_1S_{11} + W_2S_{21} + \ldots.. W_{3N}S_{3N1}$] does not correspond to the expansion of the summation in equation 8 [i.e. $Ln(I) = \sum_{i=1}^{3N} W_iS_i + C_2$]. Applicants respectfully submit that W_1S_{11} is intended to represent $W_1S_{1,1}$ and W_2S_{21} is intended to represent $W_2S_{2,1}$ and so on. The '1' subscript after the comma indicates that the S values for that equation correspond to the same intensity measurement.

The Examiner also points out that the last line does not reflect the subscript "M" (i.e. $Ln(I_M)$) but rather repeats the subscript "1" (i.e. $Ln(I_1)$). Applicants concur with the Examiner and have amended the specification to effect this correction.

The Examiner also seeks clarification on the phrase "a functional of the probe sequence" with regard to S_i. The specification discloses that S_i is a functional of the probe sequence. The method disclosed in page 18 of the specification (with respect to Figure 5), is sufficient to provide a robust value for S_i under the set of experimental conditions described in the application. No other methods are necessary.

The Examiner seeks clarification on the manner of determining the quantitative response of candidate probes, as Claim 1 requires "predicting quantitative responses of said candidate probes to the amount of their targets". Applicants respectfully submit that the specification teaches that the quantitative response (e.g., slope of the response curve) may be predicted using linear regression (e.g., from page 21, line 15 of the specification).

The Examiner also seeks clarification on the criteria by which a probe is selected or excluded, as claim 1 requires "selecting said probes from said candidate probes according to said hybridization intensities and said quantitative response". The Examiner alleges that the claim provides no cut-off value or other means to determine whether a probe would be selected or not, noting that the quality scores discussed on page 24 are not limitations of the claims. With regard to specific criteria for selection, the specification, for example, teaches that probes can be selected based upon a unified score (e.g., from page 23, line 5 of the specification). In some embodiments, the probes with the highest scores are selected. No specific cut off values are necessary.

The specification has been amended to delete blanks.

Claim 8 requires "filtering out a subset of said candidate probes, wherein said subset probes have apparent affinity constant above a threshold." The Examiner alleges that this provides a limitation for exclusion but not selection. Applicants respectfully submit that the exclusion is a method of selection and the rejected claim is not limited to methods where all remaining probes are selected.

The Office Action alleges that the unified quality score claimed in Claim 13 is not taught in greater detail. Applicants respectfully disagree and submit that exemplary methods for calculating the unified quality score is taught in great detail in the specification. For

example, in one embodiment, the specification teaches that the unified score can be a combination of quality score (based on perfect match intensity, mismatch intensity and/or slope), 3' bias score and cross hybridization score.

For these reasons, Applicants respectfully submit that the rejected claims are fully enabled by the specification. The rejection of Claims under 35 U.S.C. §112 should be withdrawn.

CONCLUSION

Applicants believe the application is now in condition for allowance and should be passed to issue. If the Examiner feels that a telephone conference would in any way expedite the prosecution of the application, please do not hesitate to call the undersigned at (408) 731-5000.

The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account 01-0431.

If the Examiner has any questions pertaining to this application, the Examiner is requested to contact the undersigned attorney.

Respectfully submitted,

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Dated: March 13, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE TO THE APPLICATION

In the Specification

Please amend the following paragraph on page 2, lines 8-14:

This application is related to U.S. Patent Application Number 09/721,042, [Attorney docket number 3367,] entitled "Methods and Computer Software Products for Predicting Nucleic Acid Hybridization Affinity", and U.S. Patent Application Number 60/252,617, [Attorney Docket Number 3373,] entitled "Methods and Computer Software Products for Selection Nucleic Acid Probes Using Dynamic Programming", filed concurrently herewith. Both applications are incorporated herein by reference for all purposes.

Please amend the following paragraph on page 16, lines 9-16:

In one aspect of the invention, a physical model that is based on the thermodynamic properties of the sequence is used to predict the array-based hybridization intensities of the sequence. Hybridization propensities may be described by energetic parameters derived from the probe sequence, and variations in hybridization and chip manufacturing conditions will result in changes in these parameters that can be detected and corrected. U.S. Patent Application Number 09/721,042, [docket Number 3367,] filed concurrently herewith and incorporated herein by reference, discloses methods for predicting nucleic acid hybridization affinity.

Please amend the following paragraph on page 17, lines 17-21:

There are a number of ways to establish the relationship between the sequence and ΔG. In preferred embodiments, one model (equation 2), shown in U.S. Application Serial Number 09/721,042, [Attorney Docket Number 3367,] previously incorporated by reference is shown below:

$$\Delta G_{seq} = \sum_{i=1}^{3N} P_i S_i \qquad \text{[Equation 2]}$$

Please amend the following paragraph on page 19, lines 1-5:

$$I = C_0\,[P \bullet T] \qquad \text{[Equation 4]}$$

$$[P \bullet T] = K_s[P][T] = e^{-\Delta G/RT}\,[P][T] \qquad \text{[Equation 5]}$$

$$\mathrm{LnI} = -\Delta G/RT + \mathrm{Ln}\{C_0[P][T]\} \qquad \text{[Equation 6]}$$

[C_2]

$$LnI = C_1 \sum_{i=1}^{3N} P_i S_i + C_2, \text{ where } C_2 =$$

$$\mathrm{Ln}\{C_0[P][T]\} \text{ and } C_1 = -1/RT \qquad \text{[Equation 7]}$$

or

$$LnI = \sum_{i=1}^{3N} C_1 P_i S_i + C_2 = \sum_{i=1}^{3N} W_i S_i + C_2 \qquad \text{[Equation 8]}$$

Please amend the following paragraph on page 19, lines 8-10:

where $W_i=C_IP_i$. The following is a linear regression model for probes of N bases in length using a training data set that contains intensity values of M probes.

$$Ln(I_1)=W_1S_{11}+W_2S_{21}+..W_{3N}S_{3N1}$$
$$Ln(I_2)=W_1S_{12}+W_2S_{22}+..W_{3N}S_{3N2}$$

.

.

.

$$Ln(I_{[1]\underline{M}})=W_1S_{11}+W_2S_{12}+..W_{3N}S_{3N1}$$

Please amend the following paragraph on page 19, lines 11-16:

Hybridization intensities (relative to a reference base, such as an A) for each type of base[s can be solved] at each position in the probe sequence may be predicted. Multiple linear regression analysis is well known in the art. See, for example, the electronic statistic book, Statsoft Inc [(http://www.statsoftinc.com/textbook/stathome.html)]; Darlington, R. B. (1990). Regression and linear models. New York: McGraw-Hill, both incorporated by reference for all purposes. Computer software packages, such as SAS, SPSS, and MatLib 5.3 provide multiple linear regression functions.

Please amend the following paragraph on page 21, lines 8-14:

where W_d is the weight for sequence based probe affinity; W_{PF} is the weight for probe formation and W_{PP} is the weight for probe dimerization. Any methods that are capable of predicting probe folding and/or probe dimerization are suitable for at least some embodiments

of the invention for predicting the hybridization intensity in at least some embodiments of the invention. In a particularly preferred embodiment, Oligowalk (available at the University of Rochester's website [http://rna.chem.rochester.edu/RNAstructure.html, last visited Nov. 3, 2000]) may be used to predict probe folding.

Please amend the following paragraph on page 23, lines 5-19:

Figure 10 shows a computer-implemented process for selecting probe sequences from a pool of candidate probes. In this particular[ly] embodiment, the sequences of a pool of candidate oligonucleotide probes are processed by a quality predictor (101). Throughout this application, the term probe may refer to the sequence of a probe. The pool of candidate oligonucleotide probes may be all possible probes against a particular target or targets. Typically, oligonucleotide probes are at least 10, 15, 20, 25 and 30 bases in length. Polynucleotide probes can be more than 10, 20, 25, 30, 100, 200, 500, 1000, or 5000 bases in length. Figure 11 illustrates a complete pool of candidate oligonucleotide probes (unfilled rectang[le]ular boxes) against a target (black rectang[le]ular box). Each of the probes is designed to be complementary to the target sequence. In this particular embodiment, the oligonucleotides are 25mers. The first probe is complementary to bases 1-25 (from the 5' end) of the target sequence. The second probe is complementary to bases 2-26 and so on. While a complete pool is often desirable, it is not necessary to have a complete pool for at least some embodiments of the invention. In some cases, filters may be used to remove some of the probes from the pool.

Please amend the following paragraph on page 24, lines 4-8:

The quality predict[a]tor is a software module that calculates quality scores (the term score refers to any qualitative and quantitative values with regard to desired properties of a probe) for probes based upon the sequences of probes. In some embodiments, the quality score may include predicted values such as perfect match intensity, mismatch intensity and/or slope.

Please amend the following paragraph on page 24, line 17-21:

In preferred embodiments, the goal of probe selection step is to find the best probes to represent a sequence. The probe selection software module takes a set of probes and a set of quality measures for each probe. It then implements an optimization algorithm to find the best n probes, spread out across the gene. Methods for probe selection using optimization algorithm is described in U.S. Application Number 09/745,965, [Docket Number 3373,] filed concurrently herewith and incorporated herein by reference in its entirety for all purposes.

Please amend the following paragraph on page 25, lines 3-16:

FIG. 12 shows another embodiment of the computer implemented probe selection process of the invention, target sequences are inputted to a candidate probe generator (121) which produce either all possible probes of certain length or a subset of the all possible probes. The candidate probe sequences are fed to the quality score predictor (122) for calculating quality measures (scores, e.g., perfect match intensity, mismatch intensity and/or slope). The candidate probe sequences are also fed to a 3' bias score predictor (123) to obtain 3' bias scores that indicates the distance of probe sequence from the 3' end of target sequence.

Since the current target preparation method is 3' biased, it is important to select probes that fall into range where its target will be made. The probe sequences may optionally be inputted into a cross hybridization score predictor (124) to calculate cross hybridization scores. The quality scores, 3' bias scores and/or cross hybridization score are combined by a probe score calculator module (125) to produce a unified score. [A probe selection module (126) picks the probes with the score which indicates that _____.]

Please amend the following paragraph on page 26, lines 7-13:

The multiple probe FASTA sequence file is also inputted into a cross hybridization predictor (136) to predict a cross hybridization score. The cross hybridization score predictor is based upon models (such as multiple linear regression models) derived from experiment data (1311). In some embodiments, cross hybridization may also be evaluated by pruning probe sequences against a human genome data base (1312) which may be residing locally, in a local area network or in a remote site such as the Genbank [(http://www.ncbi.nlm.nih.gov)].

Please amend the following paragraph on page 32, lines 8-15:

Figure 14 shows the overall process of the experiments. Yeast was used as a model system for this experiment because the yeast genome had been sequenced. Arrays containing nucleic acid probes complementary to yeast genes are commercially available from Affymetrix (Santa Clara, California)[, and include _____]. Genes were selected to cover sequence complexity such as GC content, secondary structure, Motif and gene clusters. Twenty probe pairs (perfect match and mismatch probes) were selected to

cover entire sequence of one of the 112 selected yeast genes. The probes are synthesized in situ on glass substrate using photo-directed synthesis